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*International Society
for the Study of Pleura
and Peritoneum*



COLORECTAL CANCERS

Regional Approaches: Moving Beyond PRODIGE 7

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Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura

Disclosures

- No relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

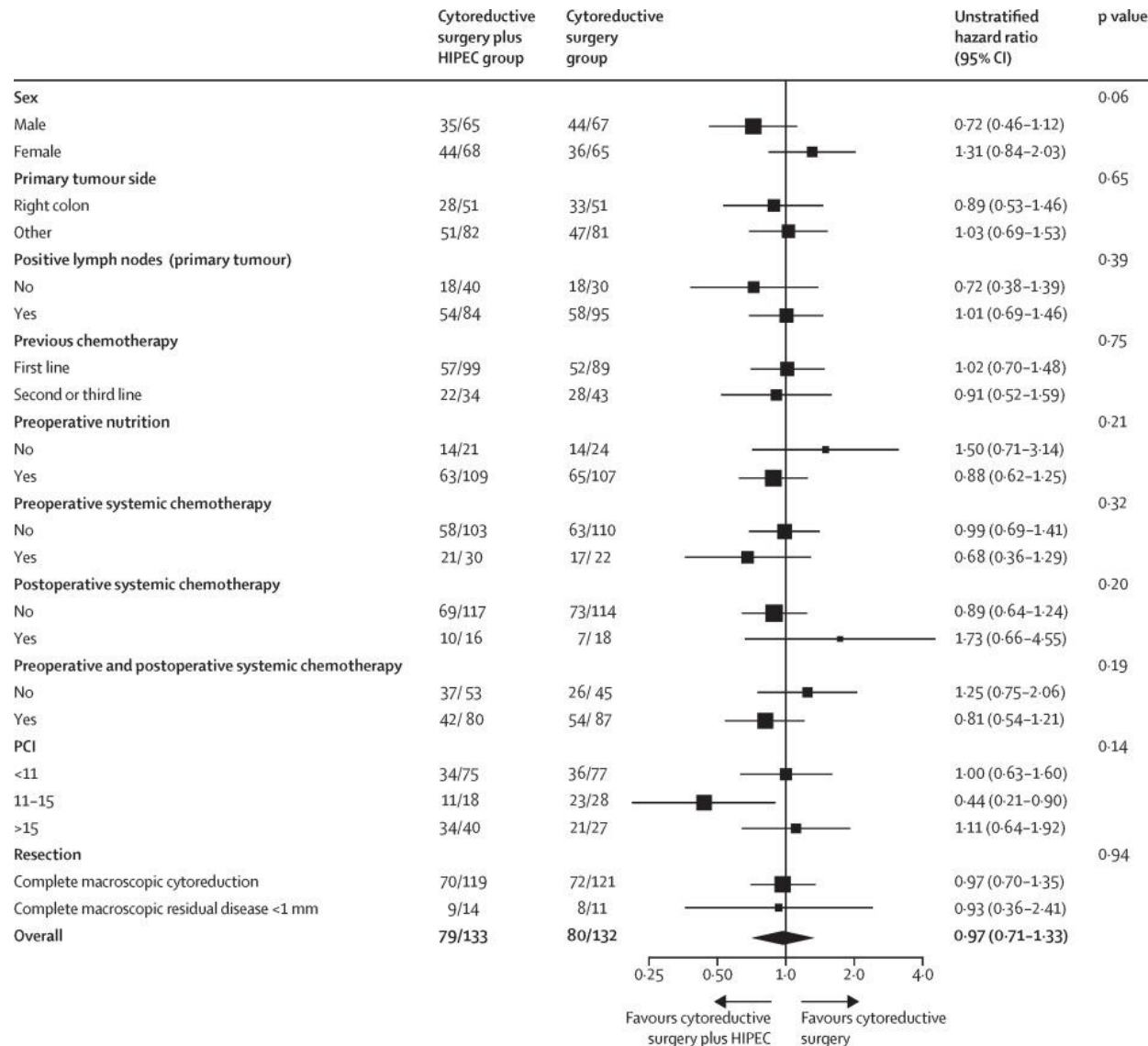
The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

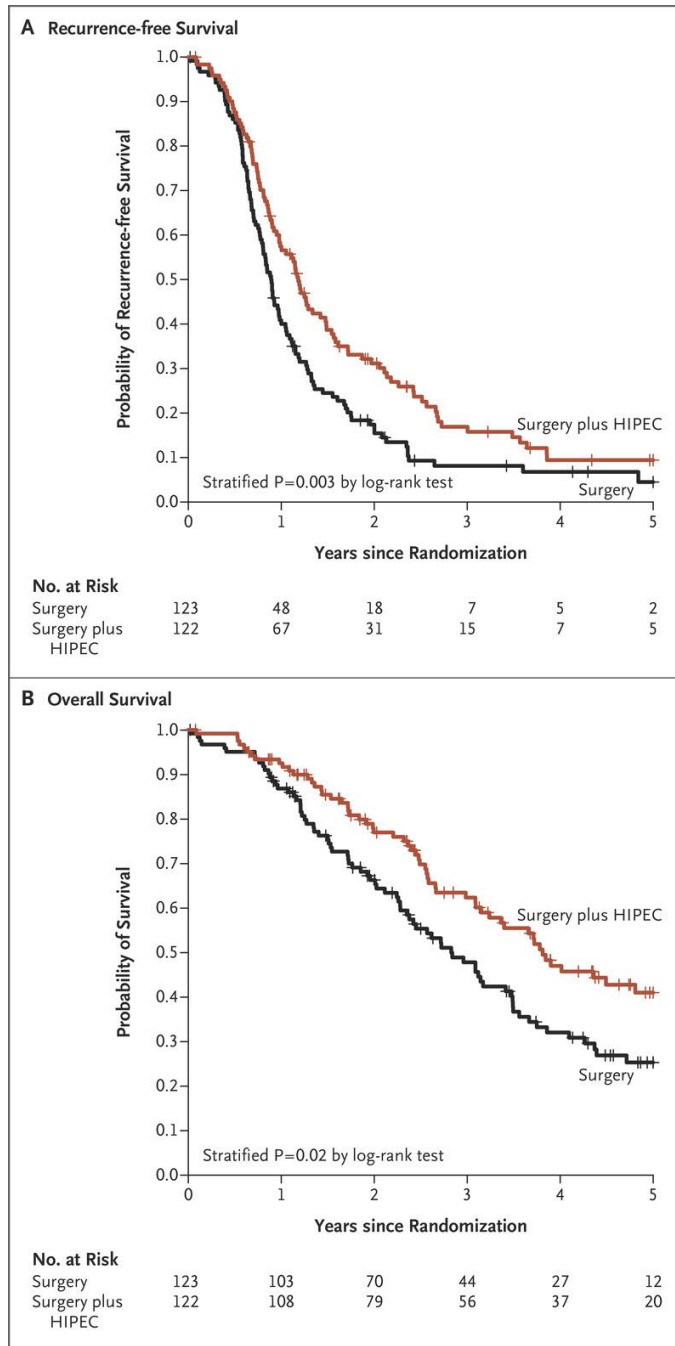
This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

PRODIGE 7 – what were the results?



Primary endpoint (OS)

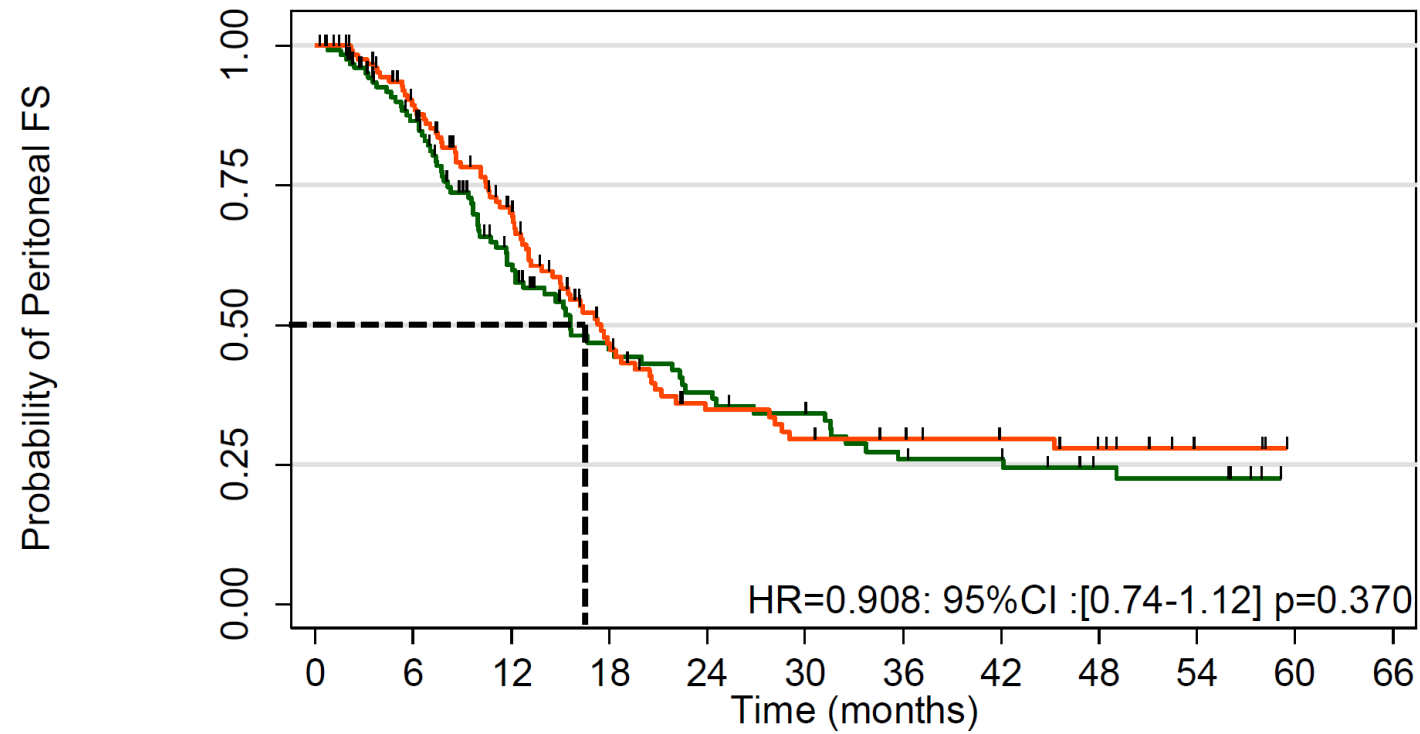
OVHIPEC-1 trial (Van Driel, NEJM 2018)



Variable	PRODIGE 7	OVHIPEC-1
Primary endpoint	OS	PFS
Median follow-up	68 months	56 months
Response rate	OX single agent: 12-24%	Pt: 60-80%
Pretreatment systemic Tx	44% OX	100% Carboplatin-Paclitaxel
Complete debulking	~ 90%	~ 68%
Perfusate	Dextrose G5%	NaCl 0.9%
Duration	30 min	90 min
Perfusion temperature	43°C	40°C

Which endpoint for a local therapy?

	Advantage	Disadvantage
Overall survival	Relevant for patients Easily measured	Confounded by intervening therapies
PFS, DFS	More impacted by locoregional therapies	Cannot be precisely measured Not always a valid surrogate for OS

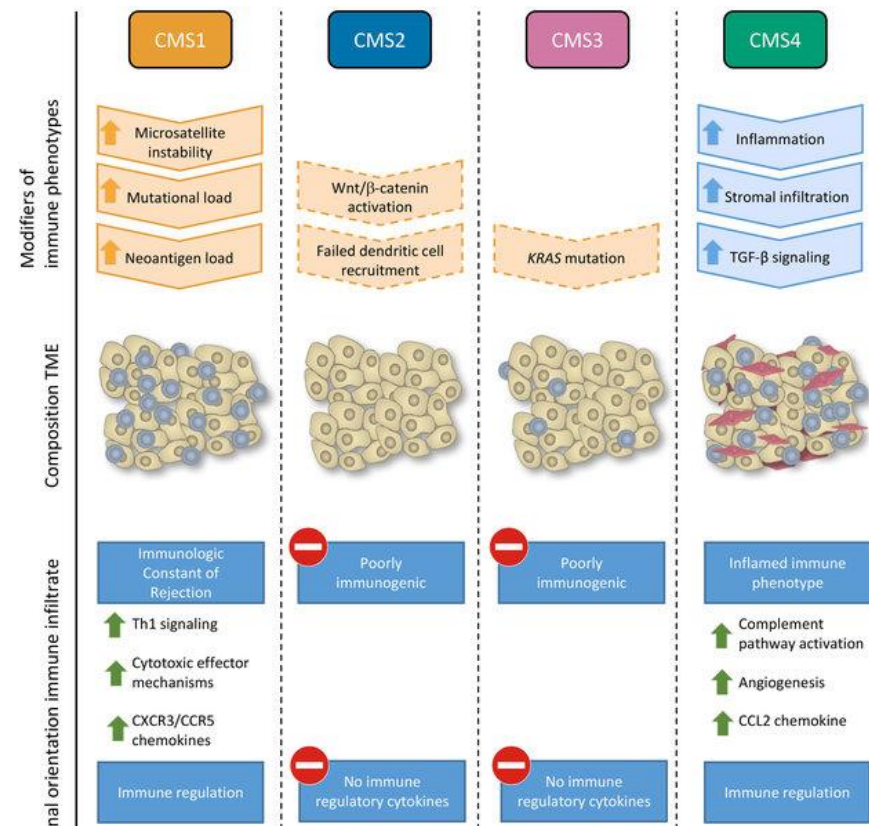


Number at risk

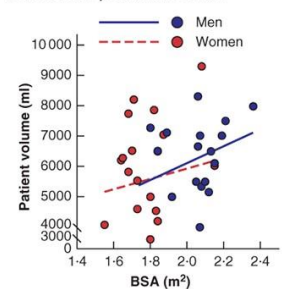
No HIPEC	132	99	59	37	30	25	19	17	13	12	7	6
HIPEC	133	107	75	41	27	23	20	18	15	10	7	5



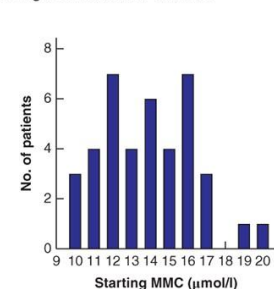
CMS 4 type: resistant to Oxaliplatin



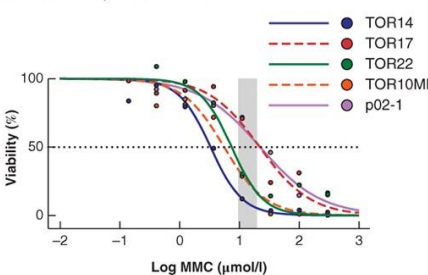
a BSA versus perfusion volume



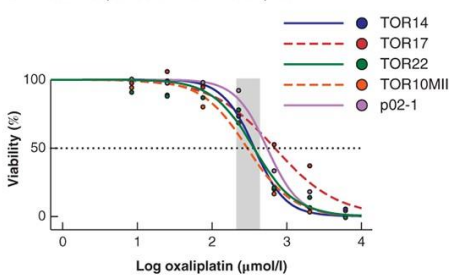
b Starting concentration of MMC



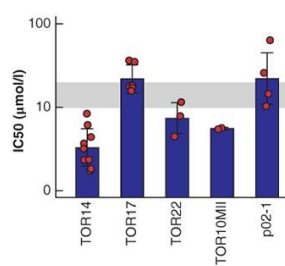
c Dose-response curve for MMC



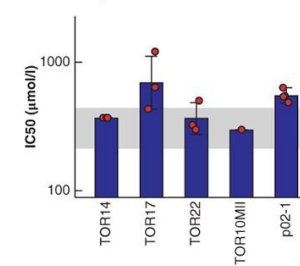
d Dose-response curve for oxaliplatin



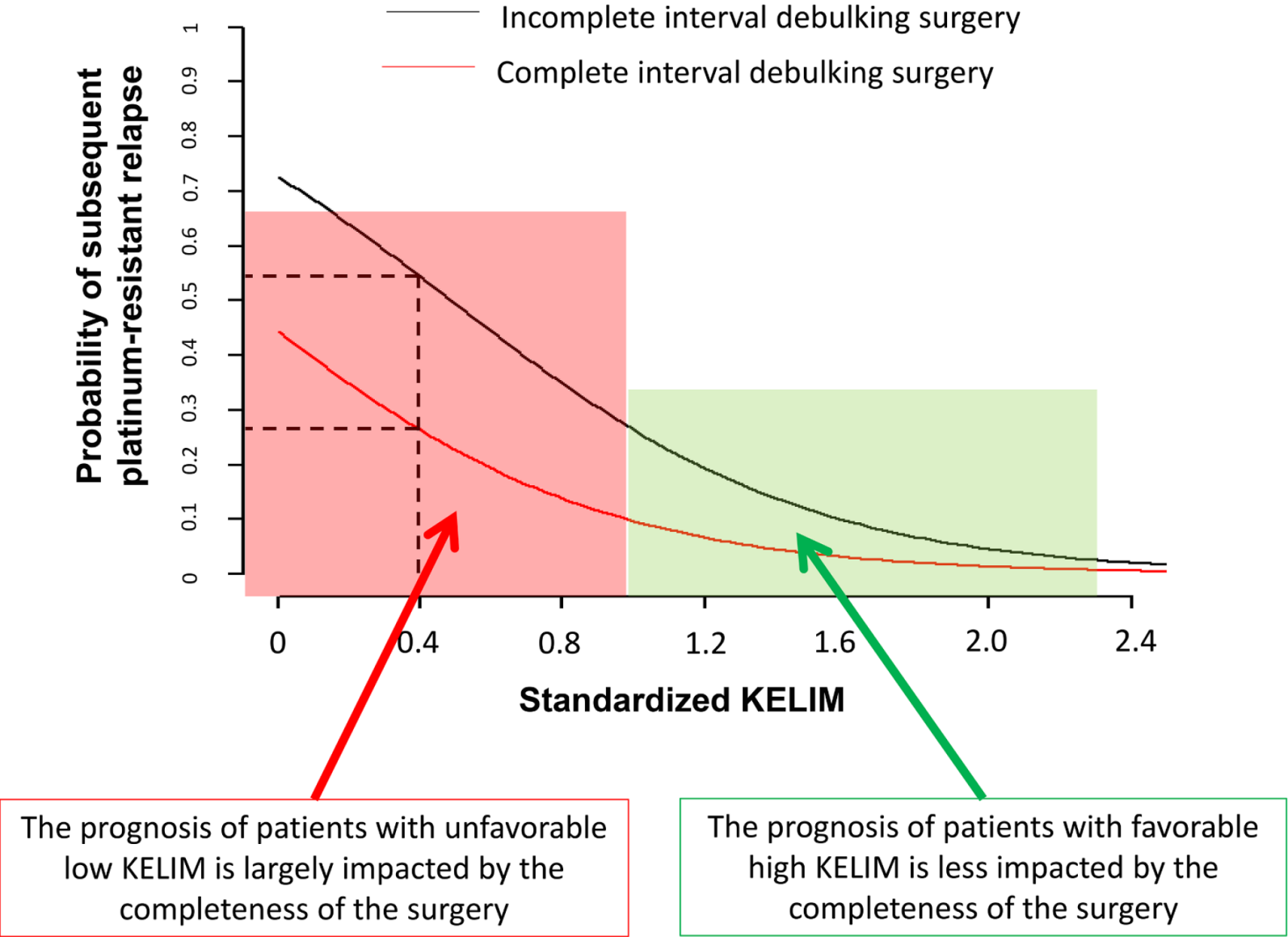
e IC50 for MMC



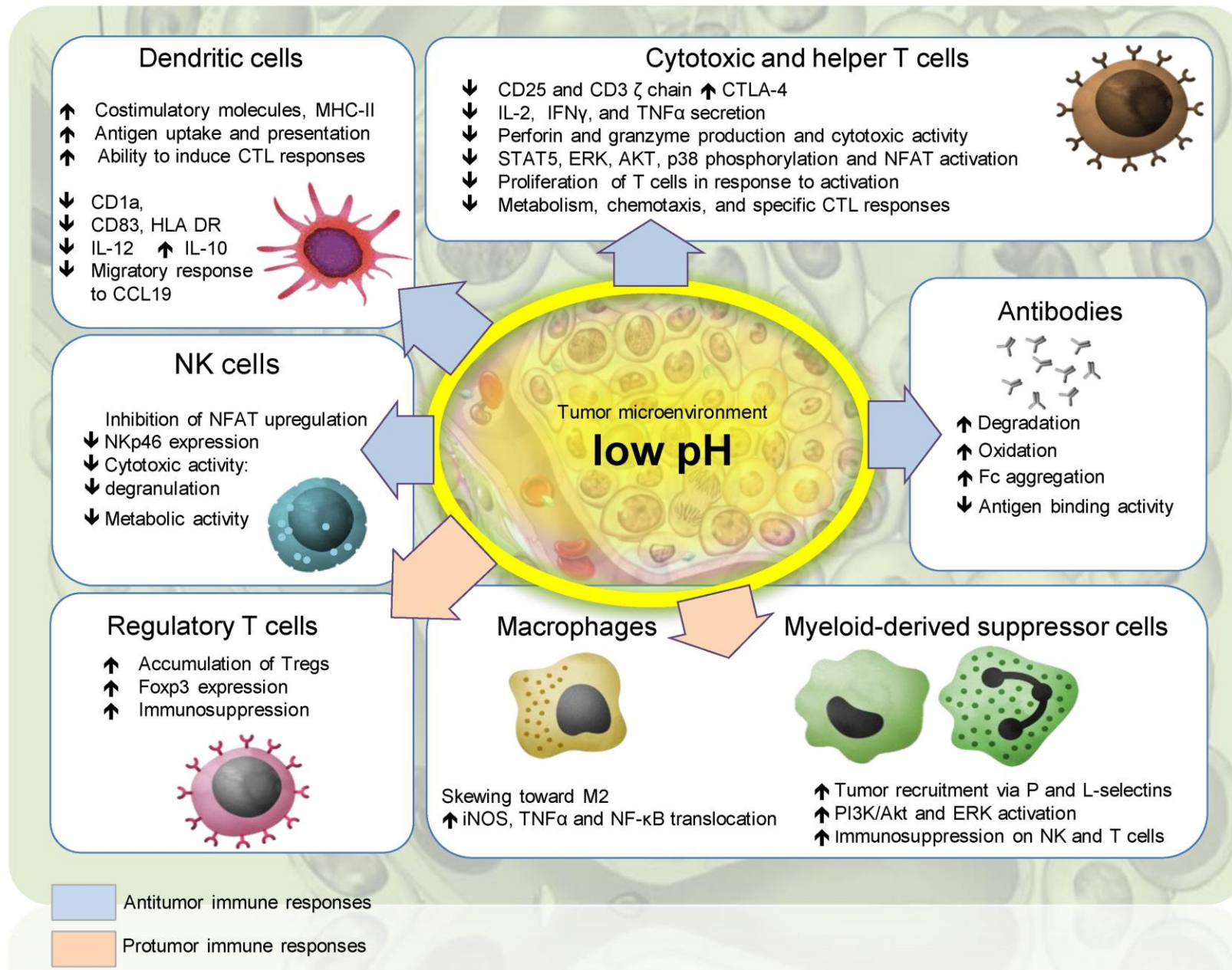
f IC50 for oxaliplatin



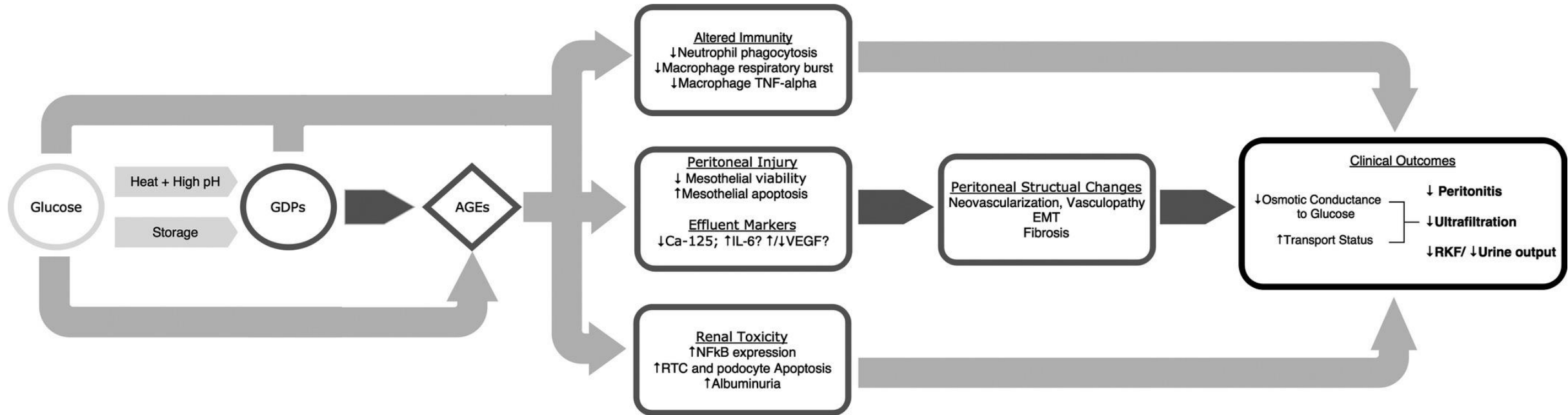
Colorectal PM PDO



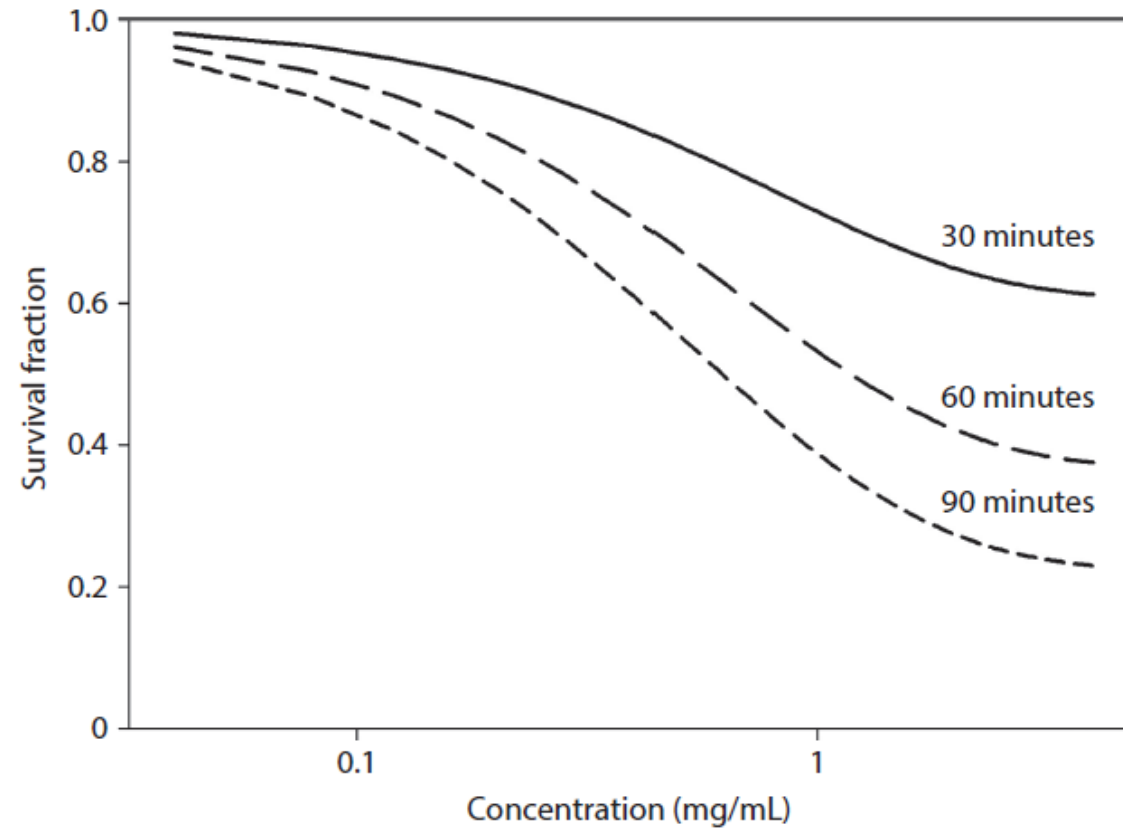
	Physioneal 40	Dextrose 5%	NaCl 0.9%	Icodextrin 4%	Plasma
Glucose %	1.36%	5%	-	-	variable
Osmolarity (mOsm/L)	344	252	308	278	308
pH	7.4	4.3	5.4	5	7.4
Na (mEq/L)	132	-	154	133	140
Cl (mEq/L)	95	-	154	96	100
Lactate (mmol/L)	15	-	-	40	1

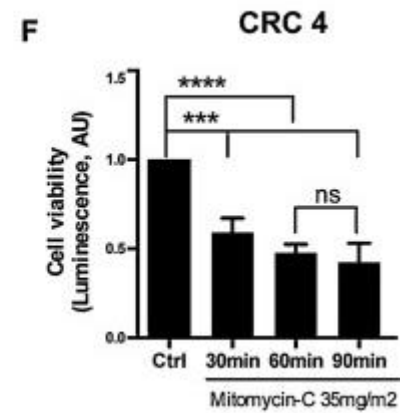
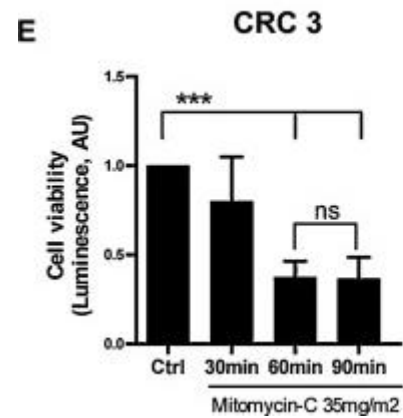
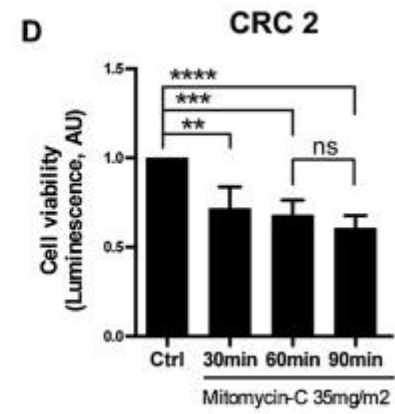
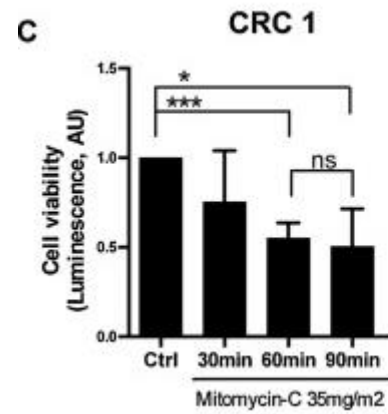


Potential adverse effects of Glucose

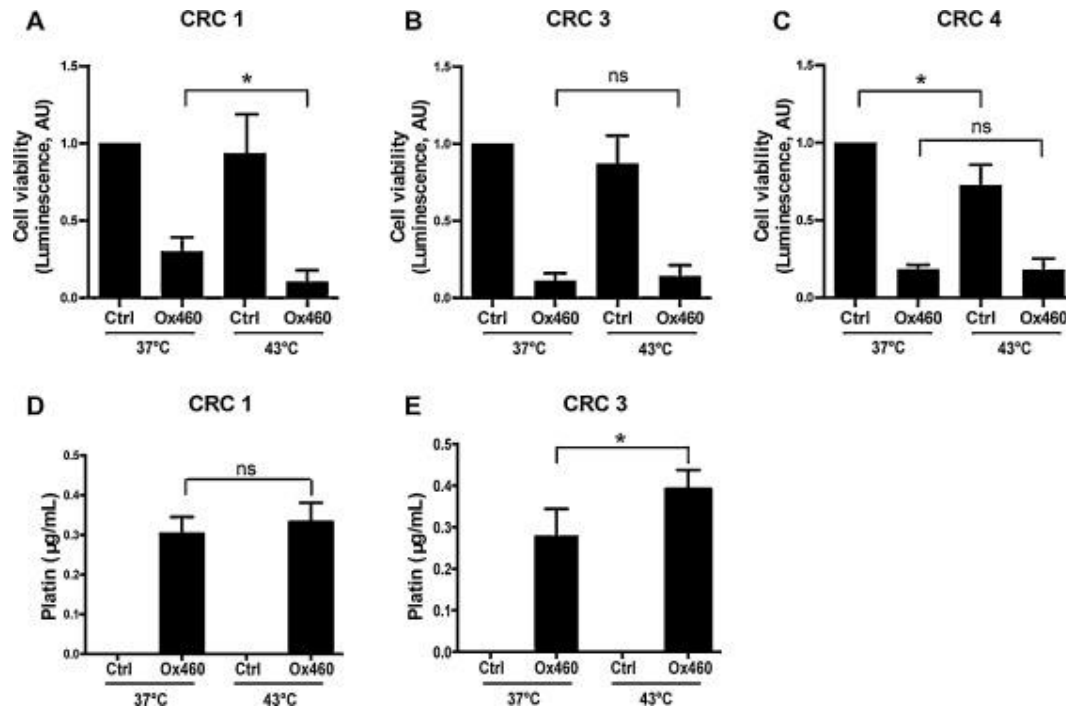


Importance of exposure time for cancer cell kill

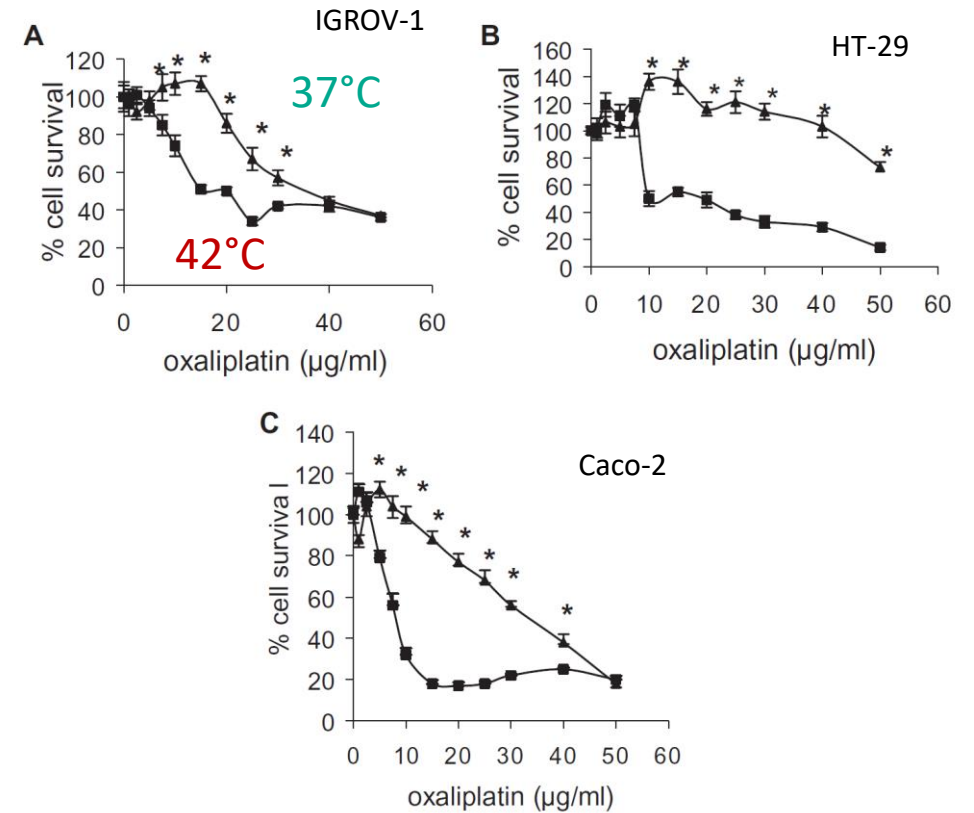




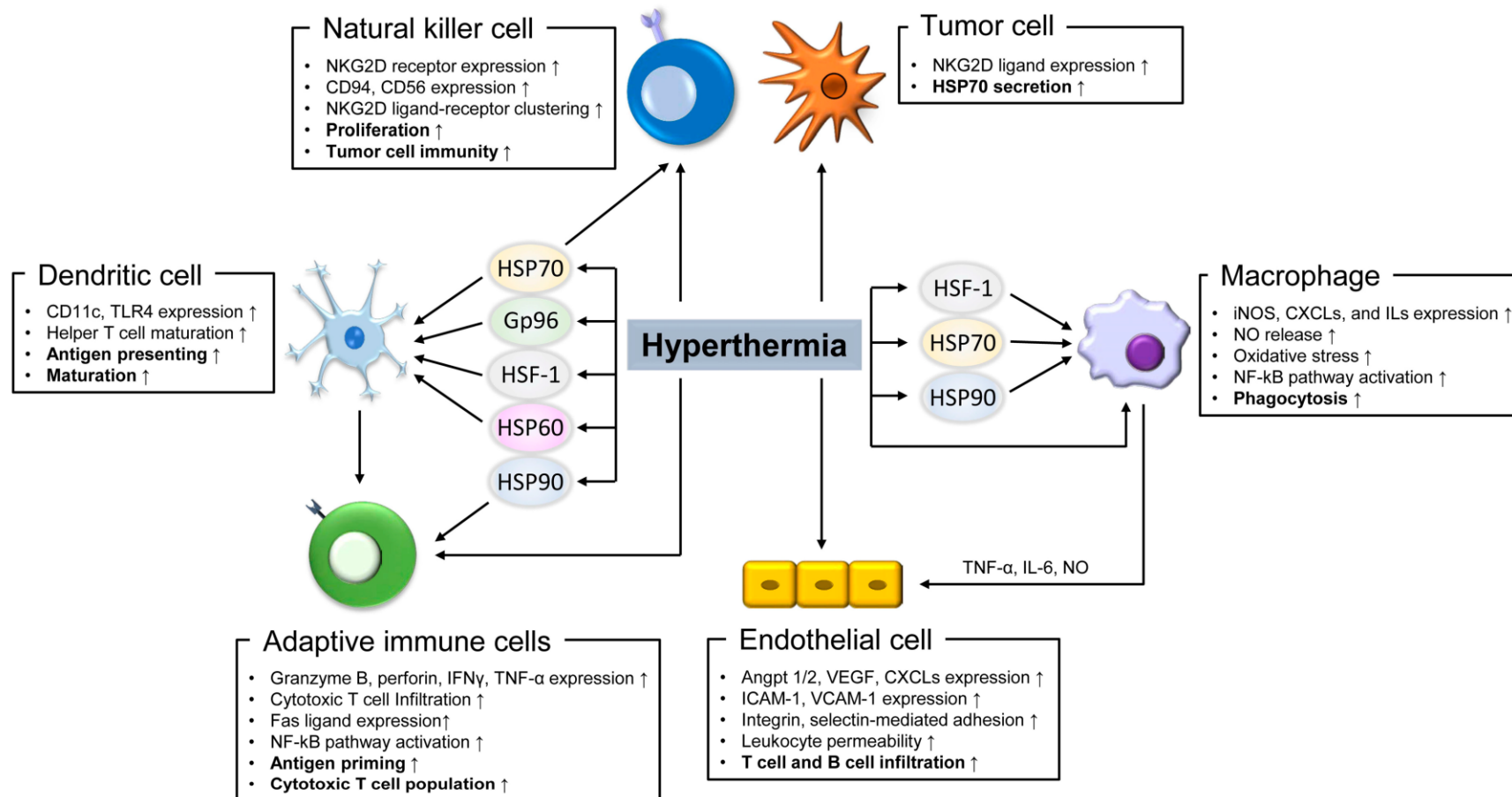
Colorectal PDX expanded organoids

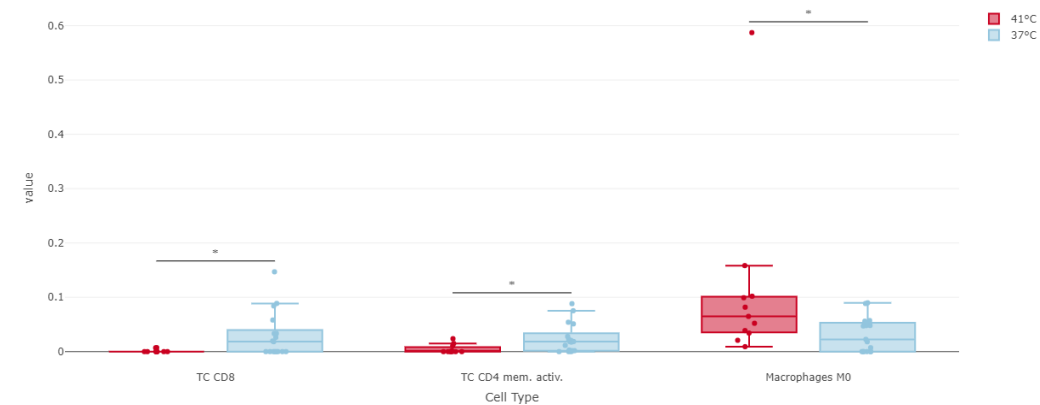
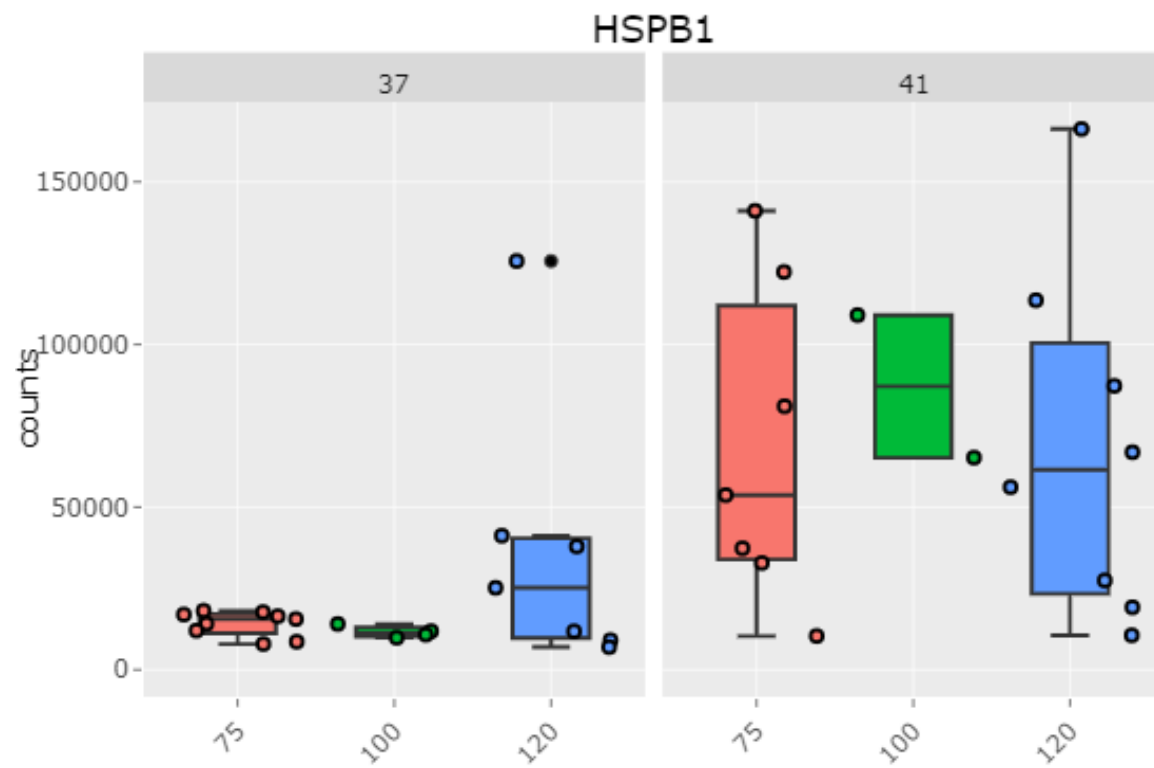


Colorectal PDX expanded organoids



In vitro cell lines





What explains the lack of effect in PRODIGE 7?

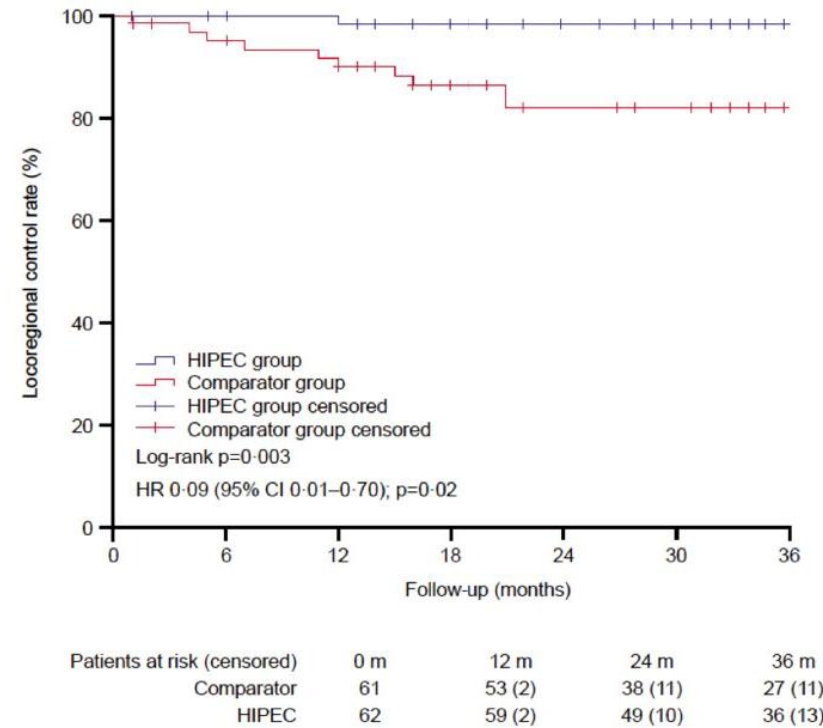
- General limitation of HIPEC: data on thermal enhancement and immune effects of mild hyperthermia limited and conflicting
- Intrinsic resistance to OX (CMS 4 type)
- Single, short duration
- Use of Dextrose 5%

What now?

- Switch to Mitomycin C, 90 min, 40°C, in NaCl 0.9% or PD solution
- Back to the drawing board: in vitro and animal studies

HIPECT4 trial

Results:



pT4 subgroup

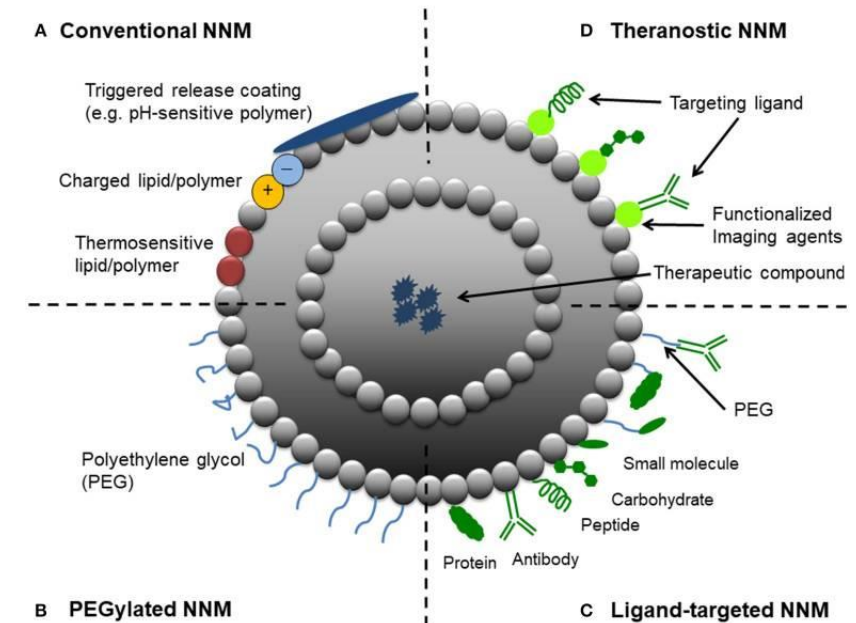
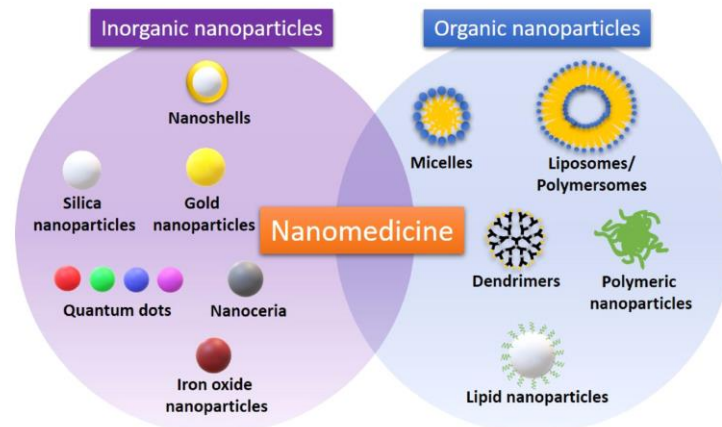
What next?

- Personalized approach: chemosensitivity testing (organoids, tumor fragments, circulating biomarkers,...)
- Prolonged IP delivery
 - Nanoparticles
 - IP hydrogels
- IP immune modulation

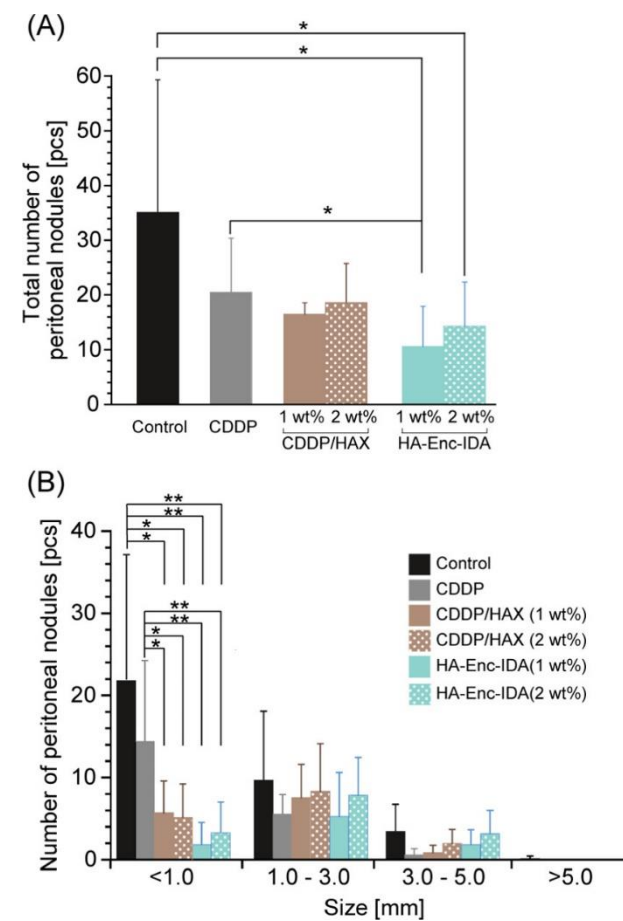
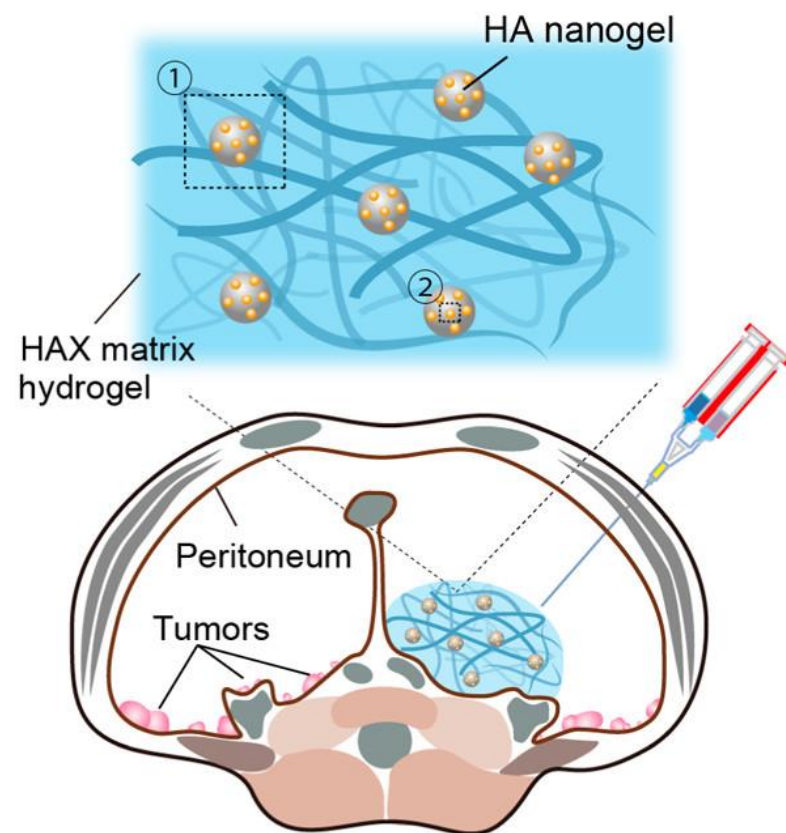
Prolonged release IPDD platforms

Table 2. The advantages and disadvantages of intraperitoneally administered drug delivery systems.

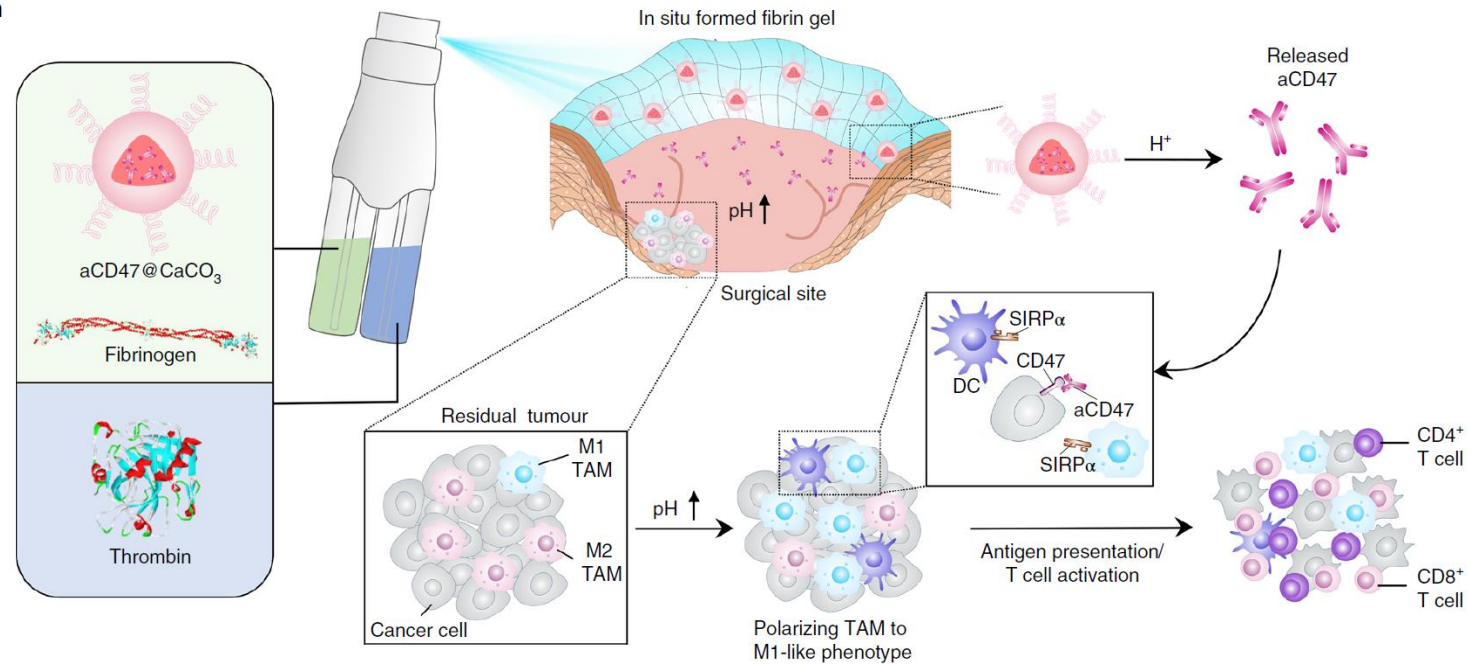
Intraperitoneal Drug Delivery Systems (DDS)	Type of DDS	Drug
Microparticulates	PLGA microparticles	Paclitaxel [77]
	Polyphosphoester microspheres (Paclimer)	Paclitaxel [78]
	Poly(ethylene glycol), poly(sebacic acid) microspheres	Paclitaxel [79]
	PLGA microspheres	[80]
Nanoparticulates	PLGA nanospheres	[80]
	Poly(lactic acid) block – hyperbranched polyglycerol (PLA-HPG) copolymer-based bioadhesive nanoparticles	Epothilone B [81]
Injectable gel-based systems	Nanoparticulate powder, Nanotax	Paclitaxel [82,83]
	Pluronic F127-Tween 80 thermosensitive mixed micelle gel	Docetaxel [84]
	Hyaluronic acid (HA) gel with micrometer scale drug precipitates	Paclitaxel [85]
	Hyaluronic acid (HA) gel with drug nanoparticle	Carboplatin [86]
	Hyaluronic acid (HA) gel with drug nanocrystals	Paclitaxel [87]
	Poly(ethylene glycol)-poly(epsilon-caprolactone)- poly (ethylene glycol) (PEG-PCL-PEG thermosensitive hydrogel with drug nanoparticles	Honokiol [88]
	Water-soluble chitosan derivative, egg phosphatidylcholine (ePC), fatty acid chloride-based injectable blend	Paclitaxel [95]
	Water soluble chitosan derivative, egg phosphatidylcholine (ePC), fatty acid chloride-based injectable blend (PoLigel)	Docetaxel [96–99]
Implants	Chitosan, egg phosphatidylcholine hydrogel film with polylactide-drug nanoparticles	Paclitaxel [89–93]
	Poly-L-lactic acid (PLLA) injection molded microdevices	Cisplatin [100]



Thermosensitive hydrogel



In situ sprayed bioresponsive immunotherapeutic gel for post-surgical cancer treatment

a

Overview of Therapeutic Strategies Aimed at Reengineering the Tumor Microenvironment of Colorectal Peritoneal Metastases

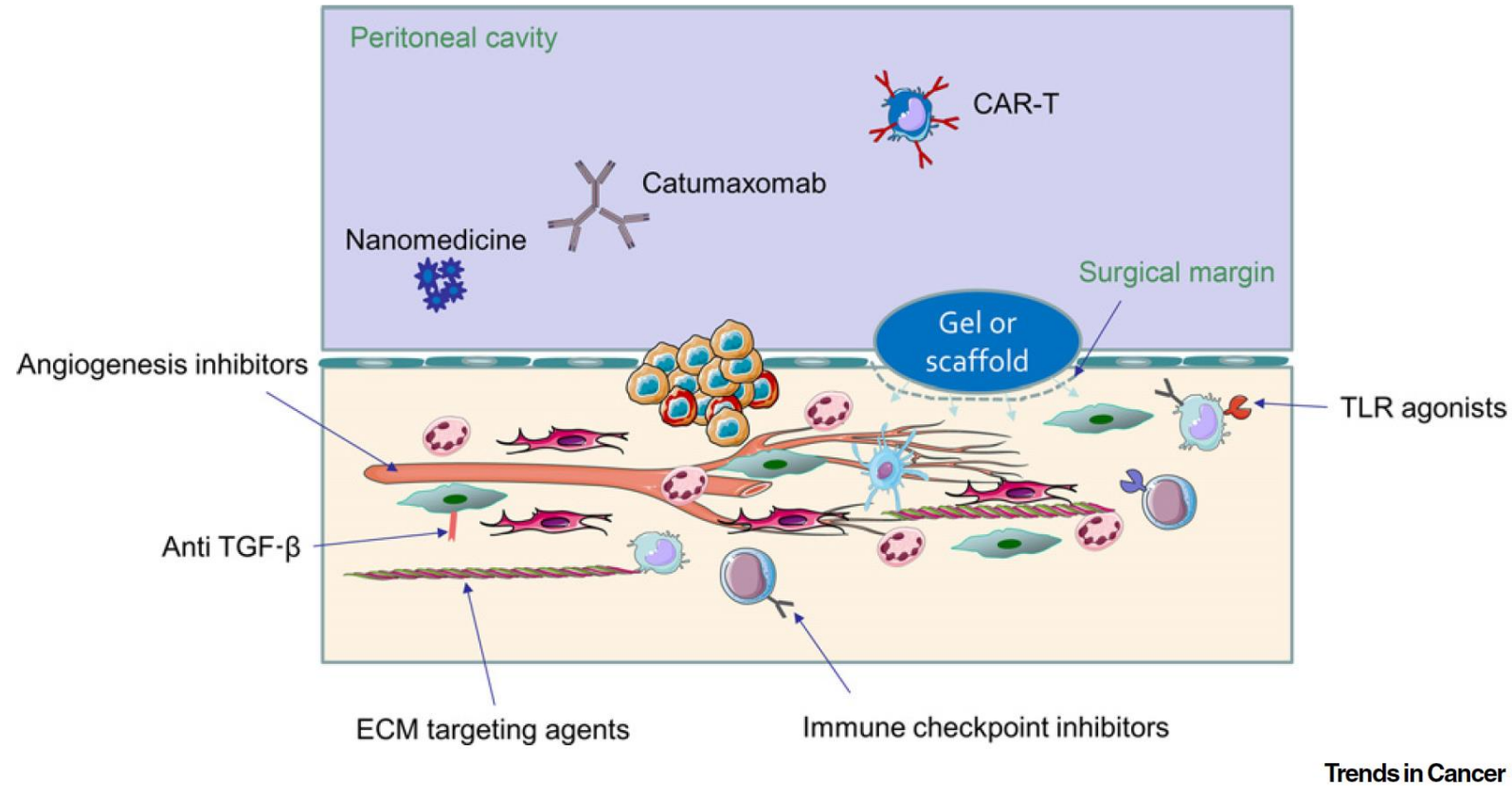


Figure 2. Abbreviations: CAR-T, chimeric antigen receptor T cell; ECM, extracellular matrix; TGF- β , transforming growth factor- β ; TLR, Toll-like receptor.

Conclusions

- Treatment of colorectal PM remains a challenge
- Recent RCTs show no benefit of HIPEC with OX
- Areas of potential progress:
 - Prolonged/metronomic delivery: gels, depots, biomaterials
 - Engineering of the TME; immune modulation
 - Personalized therapy: drug sensitivity testing